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Chemical Effects on the Activity of Eight Enzymes: A Review and a Discussion Relevant to Environmental Monitoring

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The effects of selected water pollutants and other chemicals on the activity of eight enzymes (*in vitro*) are summarized. The information may give insight into the mechanism of action of toxic chemicals and have application in the development of a rapid screening procedure involving enzymes as biomonitors in analyzing water quality.

INTRODUCTION

Many chemicals at relatively low dosages affect the metabolism of biota by altering normal enzyme activity (Hochster and Quastel, 1963; Hochster *et al.*, 1972, 1973; Webb, 1963, 1966). With some of these interactions there is high reactivity involving a high degree of inhibition of a specific enzyme that accounts for the effect on the whole animal or plant. This seems to be the case, for example, with the inhibition of δ-aminolevulinic acid dehydratase by lead salts (Goldstein, 1972) and carbonic anhydrase by acetazolamide (Wyeth and Prince, 1977). On the other hand many chemicals affect the activity of many enzymes only to a moderate degree and it is presumed that the ultimate debilitating effect on the whole organism develops from a variety of nonspecific biochemical malfunctions.

Because of high variability in analyzing enzyme–inhibitor interactions (*in vitro*) due to inconsistent factors like incubation time, purity, species and tissue differences, temperature, etc., it is difficult to compare data from different laboratories regarding the ranking of test chemicals for inhibiting (or activating) effect. This review summarizes enzyme–inhibitor data from eight related studies in order to compare the relative effects of a variety of environmental pollutants and other test chemicals on the activity of eight enzymes.

Due to the complexity and immensity of world-wide water pollution, there is a need to develop rapid and sensitive screening methods as an aid in monitoring water for the presence of biocides. Implied in this goal is the need to be alerted to conditions where multiple agents collectively cause debilitating stress on members of a biotic province where single stressor agents alone at low concentration would not be expected to cause a measurable effect. The U.S. Environmental Protection Agency is promoting specifically: (a) the development of adequate screening tests *in vitro* and *in vivo* to estimate toxic properties of environmental pollutants, (b) development of methods for determining effects on humans or experimental animals of long-term, low level exposure, (c) development of methods for

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measuring and interpreting physiological or biochemical changes occurring as precursors to disease, (d) development of personal exposure meters to improve our ability to assess exposure to air pollutants, and (e) development of biochemical exposure indicators to assess exposure by any route (Lee, 1977). The current studies on toxicant–enzyme interactions as discussed here fit into this framework. They were carried out with lactic dehydrogenase (LDH, L-lactate:NAD + oxidoreductase, EC 1.1.1.27) and glutamic-oxalacetic transaminase (GOT, L-aspartate:2-oxoglutarate aminotransferase, EC 2.6.1.1) (Christensen, 1972); carbonic anhydrase (CA, carbonate hydro-lyase, EC 4.2.1.1) (Christensen and Tucker, 1976); adenosine triphosphatase (ATPase, ATP pyrophosphohydrolase, EC 3.6.1.8) (Riedel and Christensen, 1979); acetylcholinesterase (AChE, acetylcholine acetylhydrolase, EC 3.1.1.7) (Olson and Christensen, 1980); ribonuclease (RNase, polyribonucleotide-2-oligonucleotidotransferase, EC 3.1.27.5) (Christensen and Olson, 1981a); lipase (triacylglycerol acylhydrolase, EC 3.1.1.3) (Christensen and Riedel, 1981); and urease (urea amidohydrolase, EC 3.5.1.5) (Christensen and Olson, 1981b).

Table 1 shows 141 chemicals listed with a numerical value from zero (no effect) to 5 (maximum effect) indicating their relative inhibitory effect upon the activity of from one to eight enzymes (*in vitro*). In the original reports, the results were commonly listed in terms of the molarity of the test chemical causing a 50% reduction of enzyme activity (I_{50}). The most inhibiting agents caused an effect at a minimum concentration from about 10^{-7} to 10^{-9} M. Some chemicals caused no measurable effect at the highest concentration studied, which was usually 10^{-2} M. Because most chemicals would be expected to elicit a measurable effect at some high concentration, an upper concentration limit for these test chemicals was arbitrarily set at 10^{-2} M. In many cases, especially with organic agents of low water solubility, suspensions of chemicals were analyzed at the higher concentrations or were studied in an organic solvent, with compensation made for the reagent solvent. It is not implied that the simple formulas for the inorganic chemicals shown depicts their complete chemical structure in the reaction media.

RESULTS AND DISCUSSION

Table 1 empirically ranks test chemicals in accordance with their relative effect on the activity of eight enzymes (*in vitro*). The chemicals are of different structural types which are roughly categorized. Of those tested, the inorganic and organic chemicals having the strongest inhibitory effect on each enzyme were found to be $HgCl_2$ (no organic tested) for LDH; AgCl (no organic tested) for GOT; $HgCl_2$ and acetazolamide for CA; AgCl and dicofol for ATPase; $NaAsO_2$ and eserine for AChE; $PdCl_2$ and sodium dodecyl sulfate for RNase; $HgCl_2$ and pentachlorophenol for lipase; and CH_3HgCl and 2,4-D for urease.

The salts of the highly toxic transition metals (e.g., Ag(I), Hg(II), Au(III), Pt(IV), Pd(II,IV), Cu(II)) in general caused a high inhibition for all enzymes, suggesting that these chemicals interfere with biological catalysis in a common, nonspecific way. There was a low to negligible reaction with the chloride salts of the alkaline and alkaline earth metals.

Many anions such as HPO_3^{2-}, SeO_4^{2-}, NO_3^{1-}, Cl^{1-}, Br^{1-}, and I^{1-} caused a low

TABLE 1

RELATIVE INHIBITORY EFFECT OF CHEMICALS UPON THE ACTIVITY OF GOT, LDH, CA, ATPASE, ACHE, RNASE, LIPASE, AND UREASE[a]

Chemical		Enzyme							
Common name or formula	Scientific name	GOT	LDH	CA	ATPase	AChE	RNase	Lipase	Urease
A. Inorganic chemicals (active cation)									
$AgNO_3$	—	5	5	5	5	4	5	5	5
$AlCl_3$	—	3	1	2	3	1	4	1	0
AuCl	—	—	—	—	—	4	—	—	—
$AuHCl_4 \cdot 3H_2O (AuCl_3)$	—	5	4	5	—	5	5	4	5
$BaCl_2 \cdot 2H_2O$	—	0	0	—	—	0	0	0	0
$BeCl_2$	—	3	2	1	—	1	4	—	—
$BiCl_3$	—	0	0	—	—	—	1	0	—
$CaCl_2 \cdot 2H_2O$	—	1	0	2	—	0	0	0	2
$CdCl_2 \cdot 2\ 1/2H_2O$	—	3	2	3	4	5	3	1	5
$CoCl_2 \cdot 6H_2O$	—	0	3	1	1	2	3	3	3
$CrCl_3 \cdot 6H_2O$	—	—	—	1	—	2	0	2	2
CsCl	—	0	0	—	—	—	—	—	—
$CuCl \cdot 2H_2O$	—	0	3	—	—	—	—	—	—
$CuCl_2$	—	4	4	4	5	5	4	4	5
$FeCl_2 \cdot 4H_2O$	—	0	0	—	—	0	—	3	—
$FeCl_3 \cdot 6H_2O$	—	2	2	3	—	3	4	4	0
$GaCl_3$	—	—	0	—	—	—	—	—	—
$GeCl_4$	—	2	1	—	—	—	—	—	—
$HgCl_2$	—	5	5	5	5	4	5	5	5
KCl	—	0	0	—	—	—	—	—	—
LiCl	—	0	0	—	—	—	—	1	—
$MgCl_2 \cdot 6H_2O$	—	—	0	—	—	0	0	0	0
$MnCl_2 \cdot 4H_2O$	—	0	3	3	—	—	0	0	2
MoO_3	—	0	1	—	—	—	—	—	—
$NiCl_2 \cdot 6H_2O$	—	1	0	2	2	0	3	1	4
NH_4Cl	—	—	—	—	—	0	—	—	—
$OsCl_3$	—	0	—	—	—	—	—	—	—
$Pb(NO_3)_2$	—	—	—	3	—	2	4	4	—
$PdNa_2Cl_4 (PdCl_2)$	—	5	5	5	—	5	5	5	4
$PdK_2Cl_4 (PdH_2PdCl_4)$	—	—	—	—	—	5	5	5	4
$PtK_2Cl_4 (H_2PtCl_4 \cdot 6H_2O)$	—	3	0	3	—	4	4	4	4
RbCl	—	0	0	—	—	—	—	—	—
$SbCl_3$	—	1	0	—	—	—	—	—	—
$ScCl_3$	—	0	0	—	—	—	—	—	—
$SnCl_2 \cdot 2H_2O$	—	0	0	2	—	4	—	3	—
$SnCl_4 \cdot 5H_2O$	—	—	0	3	—	4	4	3	1
$SrCl_2 \cdot 6H_2O$	—	—	0	—	—	—	—	—	—
$Th(NO_3)_4$	—	—	—	3	—	—	—	—	—

TABLE I—(*Continued*)

Chemical		Enzyme							
Common name or formula	Scientific name	GOT	LDH	CA	ATPase	AChE	RNase	Lipase	Urease
$Tl(NO_3)_3$	—	—	—	4	—	—	—	—	—
V_2O_5	—	0	0	—	—	—	—	—	—
$ZnCl_2$	—	3	3	3	—	2	0	2	2
SeO_2	—	—	—	1	—	0	—	—	—
NaCl	—	0	0	1	0	0	0	0	0
B. Inorganic chemicals (active anion)									
$NaAsO_2$	—	—	0	0	—	5	0	0	4
$Na_2HAsO_4 \cdot 7H_2O$	—	0	—	0	—	3	0	0	0
NaBr	—	—	—	—	—	—	0	0	0
$NaBH_4$	—	—	—	5	—	0	0	0	4
NaCN	—	5	0	5	—	0	0	0	0
$Na_2Cr_2O_7$	—	—	0	4	—	4	0	5	4
NaF	—	0	0	1	2	2	2	1	4
$Na_3Fe(CN)_6$	—	4	4	—	—	—	—	—	—
NaI	—	—	—	—	—	—	0	0	0
$NaIO_3$	—	—	—	3	—	4	2	1	5
NaN_3	—	4	0	4	—	1	0	0	0
$NaNO_2$	—	—	—	—	—	1	—	0	—
$NaNO_3$	—	—	—	—	—	1	—	0	—
$Na_2S \cdot 9H_2O$	—	—	—	5	0	0	0	0	0
Na_2SeO_3	—	—	—	—	—	—	0	—	3
Na_2SeO_4	—	—	—	—	—	—	0	0	1
$Na_2TeO_4 \cdot 2H_2O$	—	—	—	—	—	—	0	0	3
$Na_2HPO_3 \cdot 5H_2O$	—	—	—	—	—	0	—	—	—
C. Organometals									
Cacodylic acid	Dimethyl arsinic acid	—	—	—	—	—	—	—	2
CMBA	4-Chloromercuribenzoic acid	—	—	4	—	1	—	—	—
CH_3HgCl	Methyl mercuric chloride	—	—	4	4	3	0	2	5
$(CH_3)_2SnCl_2$	Dimethyl tin chloride	—	—	0	—	—	—	—	—
C_6H_5HgCl	Phenyl mercuric chloride	—	—	4	—	3	0	4	5
$(C_6H_5)_2Hg$	Diphenyl mercury	—	—	1	—	—	—	—	—
D. Organophosphate pesticides									
Diazinon	*O,O*-Diethyl-*O*-(2-isopropyl-4-methyl-6-pyrimidyl) phosphorothionate	—	—	3	—	3	2	2	0
Malathion	*S*-1,2-Dicarbethoxyethyl-*O,O*-dimethyldithiophosphate	—	—	—	1	3	4	4	—

Maloxon	*O,O*-Dimethyl-*S*-(1,2-dicarboethoxyethyl) phosphotothionate	—	—	—	—	5	—	—	—
Methyl parathion	*O,O*-Dimethyl-*o-p*-nitrophenyl phosphorothionate	—	—	—	—	—	—	4	—
E. Organohalide pesticides									
Aldrin	1,2,3,4,10,10-Hexachloro-1,4,4a,5,8,8a-hexahydro-endo-exo-1,4,5,8-dimethanonaphthalene	—	—	—	—	2	—	—	0
Captan	*N*-(Trichloromethylthio)-4-cyclohexane-1,2-dicarbioximide	—	—	—	—	0	0	3	0
DDT	1,1'-(2,2,2-Trichloroethylidene)bis[4-chlorobenzene]	—	—	2	3	0	1	5	0
Dicofol	Kelthane;4,4'-dichloro-α-[trichloromethyl]-benzhydrol	—	—	—	4	—	0	5	0
p-Dichlorobenzene	—	—	—	—	—	—	—	2	—
Dieldrin	1,2,3,4,10,10-Hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-endo-exo-1,4:5,8-dimethanonaphthalene	—	—	—	3	4	0	3	0
Hexachlorobenzene	—	—	—	—	—	—	—	0	—
Lindane	1,2,3,4,5,6-Hexachlorocyclohexane (isomer)	—	—	2	2	0	1	3	0
Pentachlorophenol	—	—	—	—	—	—	—	5	—
2,4,5-Trichlorophenol	—	—	—	—	—	—	—	5	1
F. Herbicides									
Bromacil	5-Bromo-3-sec-butyl-6-methyl uracil	—	—	—	—	—	—	0	—
2,4-D	2,4-Dichlorophenoxy acetic acid	—	—	—	—	—	—	0	3
Fenuron	1,1-Dimethyl-3-phenyl urea	—	—	—	—	—	—	—	0
IPC	Isopropyl-*N*-phenyl carbamate	—	—	—	—	2	3	1	0
Monuron	3-*p*-Chlorophenyl-1,1-dimethyl urea	—	—	—	—	—	—	0	—
Rootone	1-Napthalene acetamide	—	—	—	—	—	—	—	1
2,4,5-T	2,4,5-Trichlorophenoxy acetic acid	—	—	—	—	—	—	0	—
Trichloroacetic acid	—	—	—	—	—	—	—	0	—
G. Other biocides									
Acetazolamide	Diamox; *N*-Sulfamoyl-1,3,4-thiadiazole-2-yl acetamide	—	—	5	—	—	1	1	2

TABLE 1—(*Continued*)

Chemical		Enzyme							
Common name or formula	Scientific name	GOT	LDH	CA	ATPase	AChE	RNase	Lipase	Urease
Allethrin	2,2-Dimethyl-3-[2-methyl propenyl] cyclopropane carboxylic acid ester of 2 alkyl-4-hydroxy-3-methyl-2'-cyclopentenel-one	—	—	—	—	—	—	—	1
Carbaryl	Sevin; 1-Naphthyl-*N*-methyl carbamate	—	—	1	1	5	0	3	0
Eptam	*S*-Ethyl dipropylthio-carbamate	—	—	—	—	3	0	2	—
Erythromycin	—	—	—	—	—	—	0	—	—
Ferbam	Tris(dimethylcarbamodi-thioate-*S,S*)iron	—	—	—	—	—	—	2	—
Iodoacetic acid	—	—	—	2	—	1	—	1	3
Neomycin	—	—	—	—	—	—	3	0	—
Penicillamine	—	—	—	—	—	—	2	—	—
Penicillin	—	—	—	—	—	—	—	0	—
Phenacetin	*N*-(4-Ethoxyphenyl) acetic acid amide	—	—	—	—	2	—	—	—
Phenol	—	—	—	0	—	—	0	3	0
Sodium dodecyl sulfate	—	—	—	4	—	—	5	4	3
Streptomycin	—	—	—	—	—	—	2	—	—
Sulfanilamide	—	—	—	—	—	—	0	—	—
Tetracycline	—	—	—	1	—	—	—	—	—
Thiram	Tetramethylthiuran disulfide	—	—	—	—	3	4	4	0
Warfarin	3[α-Acetonylbenzyl]-4-hydroxycoumarin	—	—	—	—	—	2	5	2
H. Industrial chemicals									
Acetone	—	—	—	—	—	—	0	1	0
Aniline	—	—	—	—	—	—	0	3	0
p-Chlorobenzoic acid	—	—	—	—	—	—	—	—	3
1,2-Dichloropropionic acid	—	—	—	—	—	—	—	—	3
4,6-Dinitro-*o*-cresol	—	—	—	—	—	—	—	5	—
Ethanol	—	—	—	—	—	—	0	3	—
Methanol	—	—	—	—	—	—	—	0	0
p-Nitrophenol	—	—	—	—	—	—	—	—	1
I. Drugs and biochemicals									
Adrenaline	1,2-Methyl-amino-1-hydroxy-1-(3,4-dihydroxyphenyl) ethane	—	—	—	—	3	—	1	—
Ascorbic acid (L)	—	—	—	—	—	—	—	0	—

ATP	Adenosine-5'-triphosphate	—	—	—	—	—	—	1	—
Atropine	1-a-*H*,5a*H*-Tropan-3-a-01(±)-tropate ester	—	—	—	—	3	—	—	—
Bufotenine	*N,N*-Dimethyl-5-hydroxy tryptamine	—	—	—	—	3	—	—	—
Caffeine	1,3,7-Trimethylxanthine	—	—	—	—	3	—	—	—
Chloral hydrate	Trichloroethylidine glycol	—	—	—	—	1	—	—	—
Ergotamine	—	—	—	—	—	4	—	—	—
Eserine·SO_4	Physostigmine	—	—	0	0	5	—	—	2
Lipoic acid	—	—	—	—	—	—	—	3	—
Oubaine	Strophanthin *G*	—	—	—	3	—	—	—	—
MS-222	Ethyl-*m*-aminobenzoate methane sulfonic acid	—	—	2	—	2	2	—	0
Muscarine	2-Trimethylammonium-methyl-4-hydroxy-5-methyl-tetrahydrofuran	—	—	—	—	1	—	—	—
NAD	Nicotinamide adenine dinucleotide (oxidized)	—	—	—	—	—	—	3	—
NADH	Nicotinamide adenine dinucleotide (reduced)	—	—	—	—	—	—	4	—
Neostigmine	*m*-Hydroxyphenol trimethyl-ammonium dimethyl-carbamate	—	—	—	—	5	—	—	—
Nicotine	1-Methyl-2-(3-pyridyl)-pyrrolidine	—	—	—	—	3	—	—	—
Noradrenaline	DL-Amino-1-hydroxy-1-(3,4-dihydroxyphenol) ethane	—	—	—	—	3	—	—	—
PAM	Pyridine-2-aldoxime methiodide	—	—	—	—	1	—	—	—
Puromycin	—	—	—	—	—	—	—	1	—
Serotonin·creatinine·SO_4	5-Hydroxy tryptamine	—	—	—	—	2	—	—	—
Succinyl choline	—	—	—	—	—	1	—	—	—
Tubocurarine	—	—	—	—	—	4	—	—	—
J. Other chemicals									
EDTA·2Na·$2H_2O$	Ethylenediamine tetraacetic acid	0	0	0	—	0	5	0	1
H_2O_2	—	0	—	—	—	0	1	—	2
Piperonal butoxide	3,4-Methylenedioxy-6-propylbenzyl-*n*-butyl diethylene glycol ether	—	—	—	—	1	1	4	0
Total = 141									
Summary: (1) Total number of chemicals tested (per each enzyme)		36	40	49	19	75	66	85	68
(2) Number of chemicals eliciting some effect (each enzyme)		18	16	42	16	57	34	56	40
(3) Percentage of chemicals eliciting some effect (each enzyme)		50.0	40.0	85.7	84.2	76.0	51.5	65.9	58.8
(4) For all chemicals tested, percentage eliciting some effect upon at least 1 of the 8 enzymes		115/141 = 81.6							

* —, not tested; 0, no effect; 1, slight; 2, low; 3, medium; 4, high; 5, intense effect.

effect. However, there were distinct differences with specific anions. Sodium arsenite had a strong effect on AChE and urease but no effect on LDH, CA, RNase, and lipase. Sodium arsenate had a moderate effect upon AChE and no effect upon GOT, CA, RNase, lipase, and urease. Cyanide ion had a strong effect upon GOT and CA and no measurable effect upon RNase, AChE, LDH, lipase, and urease. Evidently, AsO_2^{1-} and CN^{1-} block some enzymes in addition to respiratory enzymes they are known to inhibit. In broad terms, the organometals had a strong effect upon CA and urease.

The organophosphate pesticides had no effect upon urease, but inhibited AChE, CA, ATPase, RNase, and lipase. Although it has been often stated that organophosphate pesticides inhibit AChE strongly and that this enzyme may be used as an indicator for this class of pollutant, the current data suggest that other enzymes are also affected. It is possible that lipase would be equally as good an indicator of organophosphate poisoning as AChE, and there may be other enzymes that are yet more sensitive. Carbamate pesticides inhibit AChE strongly as compared to the other enzymes. The carbamate, eserine, is a very strong inhibitor of AChE.

Based on the data reviewed here, lipase and ATPase appear to respond most strongly to organohalides. None of the enzymes showed a high response to the herbicides which were studied, although AChE and RNase were inhibited by the agents tested (only one in each case), and urease was inhibited by two of the four studied.

Some of the industrial organic chemicals elicited a response from lipase greater than that of the other enzymes. Many of the drugs and biochemicals analyzed had some effect on AChE and lesser effects on the other enzymes. EDTA had a strong effect on RNase, a slight effect on urease, and no effect upon GOT, LDH, CA, AChE, and lipase. The synergist, piperonal butoxide, inhibited lipase strongly, AChE and RNase weakly, and urease not at all.

Since toxic chemical pollutants often affect the activity of enzymes, at least to some degree, enzymes are logical candidates to use as biomonitors. To this end, efforts are being made to develop various types of monitoring systems using biochemicals as a test system in place of the whole animals. For example, a simple, 2-hr procedure devised to screen water for the presence of enzyme-inhibiting agents has been described (Christensen and Riedel, 1980), which involves the use of urease and AChE immobilized on the inside of glass capillary tubes. Seventy-nine percent of the 141 chemicals described would indicate a positive (inhibiting) effect if they were screened against urease and AChE. In screening against all eight enzymes, 81.6% of the 141 chemicals would indicate an inhibiting effect. Several of the chemicals studied, such as NaCl, $BaCl_2$, $CaCl_2$, and Na_2HPO_4, are essentially nontoxic and would not be expected to affect the activity of most enzymes at relatively low concentrations.

Further studies on the mechanisms of action of toxic water pollutants to provide insight regarding the primary target sites of debilitating agents would enable environmental scientists to develop logical, rapid screening systems *in vitro* that are directly correlated with toxicogenesis *in vivo*.

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